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Journal of Controlled Release, 16 (1991) 279–290

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Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (in vitro) and floating behavior (in vivo)

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(Received August 10, 1990; accepted in revised form October 24, 1990)

Microballoons with hollow structure were prepared as a novel multi-unit floating device for use in the stomach by the emulsion-solvent diffusion method. As a model drug, tranilast, an oral anti-allergic agent, was embedded in the shell of the microballoon. Tranilast and acrylic polymer, dissolved in an ethanol–dichloromethane mixture, were poured into an aqueous solution of polyvinyl alcohol with stirring to form emulsion droplets. By changing the polymer concentration in the cosolvent and the ratio of ethanol to dichloromethane, it was possible to prepare microballoons with various drug contents. With higher polymer ratios, the internal cavity volume of the microballoon increased and the drug dispersed in the shell of the microballoon became amorphous. The drug release profiles from microballoons exhibited enteric behavior. The release rate was controlled by changing the ratio of polymer to drug in the microballoon. Most of the microballoons were floatable in vitro even testing for 12 h when immersed in aqueous media, owing to their low particle density (less than unity). An in vivo radiographical study proved that microballoons orally administered to humans were dispersed in the upper part of the stomach and retained there for over 3 h against peristaltic action.

Keywords: Emulsion-solvent diffusion method; Hollow microsphere; Microballoon; Multiple-unit floating drug delivery system; Tranilast

Introduction

In previous work, we developed the emulsion-solvent diffusion process to prepare a controlled release hollow microsphere of acrylic polymer, termed a microballoon, containing the drug in its outer shell [1,2]. This device was floatable because its specific gravity was less than unity. This characteristic property encouraged us to take the project further and to develop a novel floating drug delivery system.

Most of the floating systems previously reported are single unit systems, such as the hydrodynamically balanced system (HBS) [3] and floating tablets [4,5]. These systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered,

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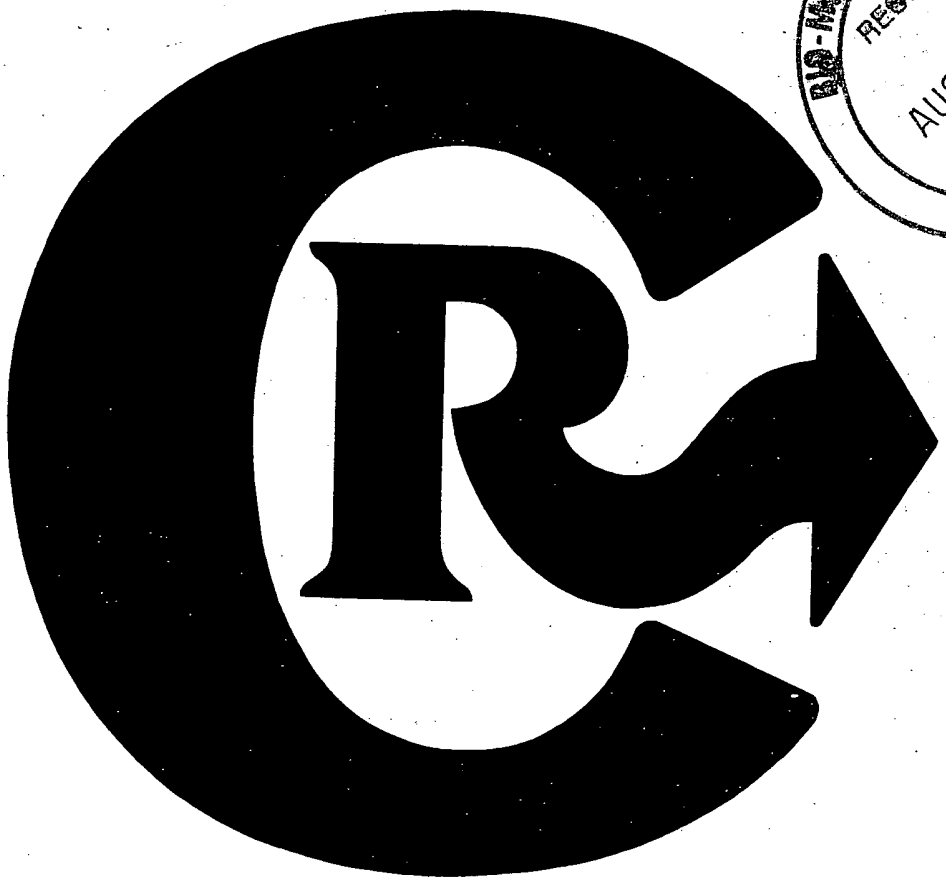

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owing to their "all-or-nothing" emptying process [6,7]. The system proposed by the present authors consists of multiple-unit floating devices. Individual units can pass randomly through the pylorus and distribute widely in the gastrointestinal tract [8,9]. Thus, reliably prolonged gastric emptying time can be expected using our microballoons.

In the present work, tranilast, an oral anti-allergic agent, was loaded in the device as a model drug in order to improve bioavailability, and thus patient compliance, by prolonging the residence time in the stomach. This compound was chosen because it is rapidly excreted in the urine and requires to be administered continuously during medical treatment for a long period (e.g. ca. 3 months) [10]. The mechanism of formation of microballoons was clarified by characterizing their micromeritic properties, i.e. surface topography, internal structure, and physicochemical behavior of the drug in the shell of the microballoon. The drug release properties of the microballoons and their floating behavior in vitro were investigated. The in vivo floating properties of the microballoons loaded with barium sulfate were also tested radiographically in the stomach of volunteers to estimate dispersibility in the gastrointestinal tract.

Materials and Methods

Preparation of microballoons

The apparatus for preparation of microballoons was fully described in a previous paper [11]. Tranilast (Tran; Siratori Pharm. Co., Ltd., Japan, melting point = 210°C) and enteric polymer were codissolved at room temperature in an ethanol–dichloromethane mixture (1:1 v/v) which was finely dispersed in aqueous medium. The polymer used was Eudragit S100 (Eud.S) from Röhm Pharma. GmbH (Germany), which was soluble in alkaline solution (pH > 7.0) and in alcohol. The dispersed phase was poured into a stirred aqueous medium containing 0.75% (w/v) of polyvinyl alcohol (PVA-120; Kuraray Co., Ltd., Japan) thermally controlled at 40°C. The representative formulations for preparation of microballoons are given in Table 1. Agitation was provided by a propeller-type stirrer (Heidon 600G; Shinto Kagaku Co., Ltd., Japan) operating at 300 rpm, by which the poured solution was finely dispersed into discrete droplets, forming an oil-in-water (O/W) type emulsion. The preferential diffusion of ethanol from the droplets into the medium induced the coprecipitation of the polymer and the drug on the outer surface of the droplet. The remaining dichloromethane was enclosed in the droplet by a film-like shell of coprecipitated polymer and drug. A gaseous phase was produced inside the shell by the evaporation of dichloromethane during agitation of the system. Further gradual counterdiffusion of dichloromethane and water through the film shell promoted the solidification of the droplets entrapping the gas phase. The evaporated dichloromethane was removed from the system by aspiration and was replaced by water. After agitation for 60 min, the solidified microballoons with a hollow structure containing water were recovered by filtration, washed with water and dried in an oven (KCV-4D; Advantec, Japan) at 120°C for 2 h. During the drying process, an air cavity was produced inside the spheres, producing the microballoons. It was found that the drug in the shell of the microballoons after drying was present as the anhydride, which was the stable form, determined by the X-ray analysis in Fig. 3.

TABLE 1

Formulations for preparation of tranilast microballoons

Tran:Eud.S ratio	Inner solvent phase		Outer water phase[a]
	Tran+Eud.S (g)	CH_2Cl_2+EtOH (ml)	Polyvinyl alcohol soln. (0.75% w/v)
1:2	0.5+1.0	5+5	200 ml
1:3	0.4+1.2	6+6	200 ml
1:4	0.4+1.6	8+8	200 ml

[a]Warmed to 40°C and agitated at 300 rpm.
After agitation for 60 min, the products were filtered off and dried in an oven (120°C, 2 h).

Physicochemical properties of microballoons

The average diameter and the weight recovery of microballoons were measured. The recovery percentage was defined as the weight ratio of −12 mesh (sieve aperture 1410 μm) fraction of the microballoons to the amount of solid raw materials formulated, multiplied by 100. The average diameter was represented by the geometric mean diameter obtained by a sieve method. The surface morphology and the internal structure of the microballoons were observed by a scanning electron microscope (JSM-T330A; Nihon Denshi Co., Ltd., Japan). The crystalline form of tranilast dispersed in the crust of microballoon was analyzed by using an X-ray powder diffractometer (RAD-IC, Rigaku, Japan; Ni filter, Cu $K\alpha$, 30 kV, 30 mA; scanning speed 2°/min) and a differential scanning calorimeter (model CN808521; Rigaku, Japan; range ±8 mcal/s) at a heating rate of 10°C/min under a dry nitrogen flow of 35 ml/min. The tranilast content in the microballoons was determined as follows. The sample (accurately weighed) was dissolved in 100 ml of dimethylformamide. After filtration, a portion of the resulting solution was diluted appropriately. The solution was assayed spectrophotometrically at 335 nm (model 320, Hitachi Manufacturing, Tokyo). The polymer used did not interfere in the assay.

Characterization of hollow structure of microballoons

The hollow structure of the microballoons was estimated by measuring the particle density (ρ_p) by two methods, viz., a photographic counting method and a liquid-displacement method. With the photographic counting method, an image analyzer (IBAS, Carl Zeiss, Germany) was used to determine the volume (V) of n particles (of weight W) for use in eqn. (1)

$$\rho_p = W/V = W/(\sum^{n} \pi d^3/6) \quad (1)$$

where d is the diameter of the projected image of the microballoon. With the liquid-displacement method, the weighed microballoons were immersed in an aqueous solution (0.02%, w/v) of Tween 20 in a pycnometer (25 ml) at 20°C. The porosity (ϵ) and the ratio of diameter to shell thickness (D/T) of the microballoons were used as the other parameters for characterizing the microballoons:

$$\epsilon = (1 - \rho_p/\rho_t) \times 100 \quad (2)$$

$$D/T = 2/[1 - (\epsilon/100)^{1/3}] \quad (3)$$

where ρ_t is the true density measured using a helium–air pycnometer (model 1302, Micromeritics Instrument Co., USA). The pore size distribution in the microballoons was measured by the mercury displacement method at various pressures employing a porosimeter (Poresizer 9305, Shimazu Co., Ltd., Japan).

Drug release property of microballoons

The fractionated microballoons (150–250, 250–297, 297–500, and 500–1000 μm) containing 50 mg of tranilast were tested using the dissolution test apparatus specified in the USP XXII (NTR-VS3, Toyama Sangyo Co., Ltd., Japan). The samples were gently spread over the surface of the dissolution medium (disintegration test solution No. 2, of pH 6.8, composed of NaOH and KH_2PO_4, or the phosphate buffer of pH 7.2 specified in the Japanese Pharmacopeia XI), stirred by a paddle rotated at 100 rpm and maintained at 37°C. Samples withdrawn at suitable intervals from the dissolution vessel were filtered and assayed spectrophotometrically at 335 nm to determine the dissolved drug concentration. After the drug release test, the microballoons were recovered to investigate their surface topography and internal texture with a scanning electron microscope.

In vitro floating test

The floating test on the microballoons was carried out using the dissolution method II apparatus specified in the USP XXII. The microballoons (fractionated to 297–500 and 500–1000 μm; weight 300 mg) were spread over the surface of the dispersing medium (900 ml, 37°C), which

was agitated by a paddle rotated at 100 rpm. Disintegration test solution No. 1 (pH 1.2) containing Tween 20 (0.02%, w/v) was used as dispersing medium to simulate gastric fluid. After agitation for a previously determined interval, the microballoons that floated over the surface of medium and those that settled to the bottom of the flask were recovered separately. After drying, each fraction of the microballoons was weighed. The buoyancy of the microballoons was represented by the following equation:

$$\text{buoyancy}\ (\%) = Q_f/(Q_f+Q_s)\times 100 \qquad (4)$$

where Q_f and Q_s are the weights of the floating and the settled microballoons, respectively. As control granules, microspheres of Eudragit RS containing barium sulfate were prepared according to the method previously reported [11] and the floating test was carried out analogously.

In vivo radiographical study

Tranilast microballoons made with Eudragit S containing barium sulfate as a contrast agent were prepared for the radiographical in vivo test. The study was carried out with two healthy male volunteers free of detectable gastrointestinal diseases or disorders. Each subject, having fasted overnight, had a light Japanese breakfast (one rice ball and one cup of soup). After 30 min, each subject ingested two hard-gelatin capsules packed with microballoons (1000 mg) together with 100 ml of water. The intragastric behavior of the microballoons after dosing was observed by taking a series of X-ray photographs at suitable intervals.

Results and discussion

Formation of microballoons

Preliminary tests proved that the stable formation of an O/W emulsion at the initial stage and the precipitation of polymer on the surface of the dispersed droplet were the key factors in preparing desirable microballoons having a smooth outer surface and low density. To satisfy this requirement, the combination of an acrylic resin, Eudragit S, and a mixed solvent of ethanol and dichloromethane was chosen. Ethanol and dichloromethane are good and poor solvents for Eudragit S, respectively. The polymer and the drug were soluble in the mixture of ethanol and dichloromethane. The mixing volume ratio of ethanol to dichloromethane (1:1) was the most suitable for producing the stable emulsion in the aqueous medium. The counterdiffusion of ethanol and water through the interface between the emulsion droplet and the aqueous medium reduced the solubility of the polymer at the interface with the droplet, inducing precipitation of the polymer on the surface of the emulsion droplet. The dispersed droplet was enclosed with a film-like shell of the polymer. The present solvent system differed from that used in the preparation of microcapsules by the solvent evaporation method, in which dichloromethane has been frequently used as a good solvent for the polymer [12,13].

The polymer concentration in the mixed solvent was another important factor in producing microballoons successfully. With increasing concentration of the polymer, the size of the microballoons increased, but the recoveries of microballoons decreased drastically when the concentration exceeded ca. 0.12 g/ml. At a polymer concentration of 0.1 g/ml, the recovery of spherical microballoons attained its maximum (e.g. 75–79 wt%). The average diameter of the microballoons was around 350 μm irrespective of the formulation, as shown in Table 2. The

TABLE 2

Effect of initial tranilast/Eudragit S ratio on recovery, size and drug content of resultant microballoons

Tran:Eud.S ratio	Recovery[a] (wt.%)	D_{50}^{b} (μm)	Drug content (wt.%)		Incorporation efficiency (%)
			Theoretical	Found	
1:2	76.0	338	33.3	31.5	94.6
1:3	75.3	344	25.0	23.2	92.6
1:4	78.9	333	20.0	18.4	92.1

[a]Percentage of −12 mesh (aperture 1410 μm) fraction of microballoons recovered.

[b]Geometric mean diameter on log probability plot by sieving method.

Fig. 1.

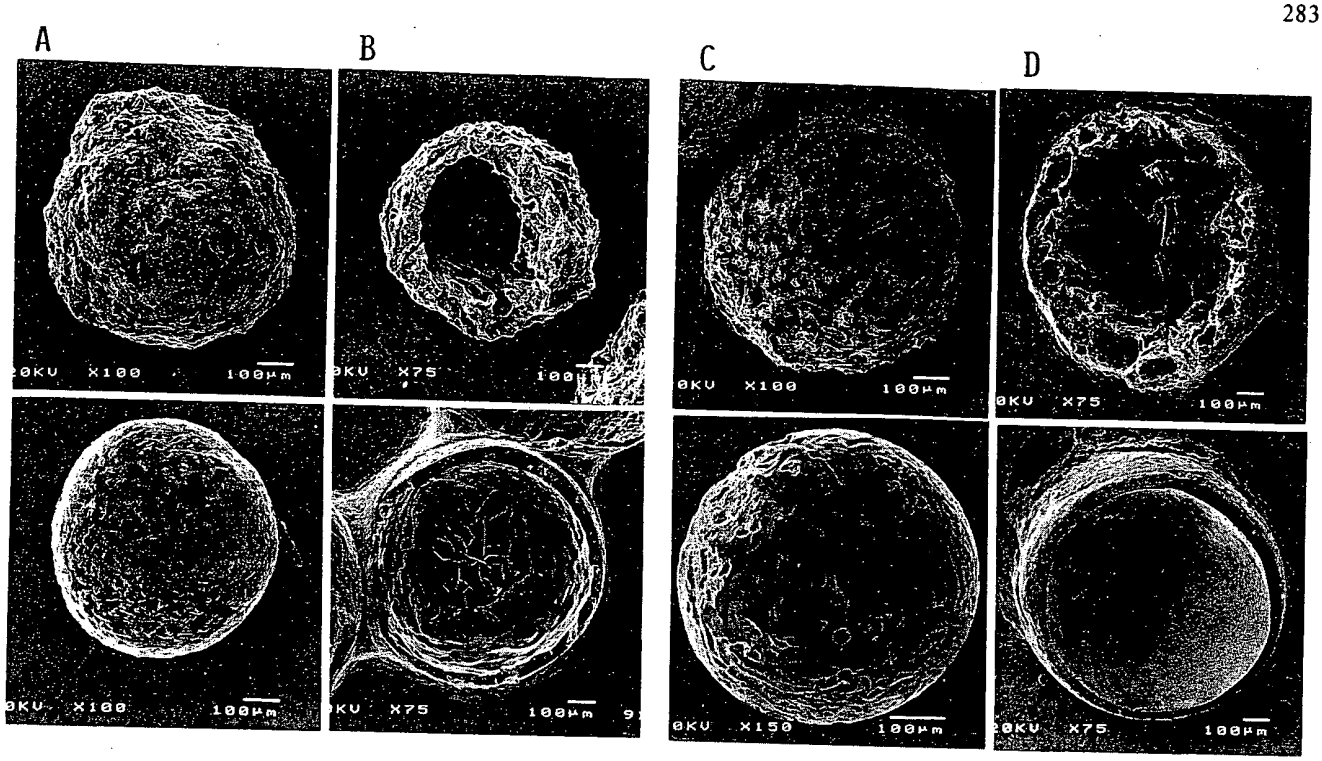

Fig. 1. Scanning electron microphotographs of tranilast microballoons before (A,B) and after (C,D) the dissolution test. Tranilast: Eudragit S ratio: top, 1:2; bottom, 1:4.

loading of the drug into the microballoons was higher than 90% irrespective of the microballoon size and the formulation. This small drug loss was accounted for by the slight solubility of tranilast in polyvinyl alcohol solution mixed with ethanol.

The surface topography and the internal structure of microballoons were investigated with a scanning electron microscope, as shown in Figs. 1A and 1B, respectively; the figures reveal that the microballoon had a spherical shape and a round cavity enclosed by an outer shell composed of the drug and the polymer. By increasing the ratio of polymer to tranilast, microballoons having a smooth surface and a rigid thin shell were prepared, since the drug concentration in the mixed solvent decreased. The microballoons prepared with a tranilast: Eudragit S ratio of 1:4 had a film-like shell without any visible pores, in contrast to microballoons with tranilast: Eudragit S = 1:2, as shown by their cross sections (Fig. 1B). The floating property of a microballoon closely depended on its internal structure, as discussed later.

Identification of hollow structure of microballoons

The particle densities measured by the counting and the displacement methods were smaller than unity (which is the specific gravity of gastric fluid) for all formulations (Table 3). The differences between the data for the two methods were due to the intrusion of aqueous solution into the pores of the shell in the displacement method. The data measured by the displacement method were more reasonable for describing the buoyancy because the experimental conditions were similar to those inside the stomach. The density decreased with the increase of the polymer concentration in the formulation, as clearly seen in the cross section of the microballoons in Fig. 1B. The ratio of diameter to shell thickness of microballoons (D/T) measured from the photographic image (SEM) of the cross section was 8.9 and 14.4 for weight ratios of drug to polymer = 1:2 and 1:4 in the formulation, respectively (Fig. 1B). These values agreed well with the D/T values obtained by

TABLE 3

Particle density, porosity and ratio of diameter to shell thickness of tranilast microballoons measured by counting or displacement method

Tran:Eud.S ratio	Size fraction (μm)	Counting[a]			Displacement[b]		
		Density (g/cm³)	Porosity (%)	D/T[c] (−)	Density (g/cm³)	Porosity (%)	D/T[c] (−)
1:2	297– 500	0.712	45.8	8.7	0.850	35.3	6.8
	500–1000	0.634	51.7	10.1	0.655	50.1	9.7
1:3	297– 500	0.654	50.1	9.7	0.750	42.8	8.1
	500–1000	0.567	56.7	11.6	0.543	58.6	12.2
1:4	297– 500	0.607	53.6	10.7	0.710	45.7	8.7
	500–1000	0.516	60.6	13.8	0.553	57.7	12.0

[a]Measured by photographic counting method.
[b]Measured by Tween 20 aqueous solution (0.02%) displacement method.
[c]D/T=diameter/shell thickness.

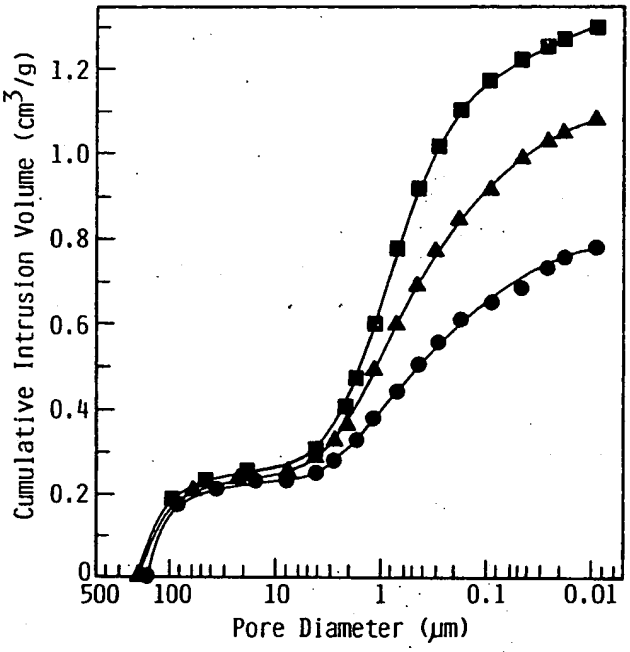

Fig. 2. Cumulative pore size distribution of microballoons prepared with various ratios of tranilast to Eudragit S. Key: (●) 1:2; (▲) 1:3; (■) 1:4. Size fraction: 500–1000 μm.

the counting method as shown in Table 3.

The internal cavity volume of the microballoons (diameter 500–1000 μm) was also measured quantitatively by the mercury displacement method. The intrusion volume of mercury for microballoons having a polymer to drug weight ratio=1:4 was higher than that for the weight ratio=1:2, as shown in Fig. 2. The intrusion volume increased markedly over the pore diameter range from 0.1 to 3 μm, which indicated the pore size in the shell of the microballoon. The pore volume found corresponded to the volume of mercury intruded into the hollow cavity through the pores in the shell. This finding suggested that the internal cavity was completely enclosed within the rigid shell, as shown by the cross sections of the microballoons. The porosities of microballoons calculated from the intrusion volume of mercury were 46.8, 52.2 and 57.8% for a weight ratio of drug to polymer=1:2, 1:3 and 1:4, respectively, in the formulation. These values agreed with the porosity data obtained by the water-displacement method (Table 3).

Crystalline form of tranilast dispersed in the shell of microballoons

Figure 3 shows the X-ray powder diffraction patterns (A) and DSC thermograms (B) for the microballoons crushed with an agate mortar and pestle and for a physical mixture of raw crystals of drug and polymer. The characteristic X-ray diffraction peaks of the drug and the endothermic peak due to melting of tranilast in the microballoon weakened with increase of the polymer to drug ratio. The disappearance of the X-ray

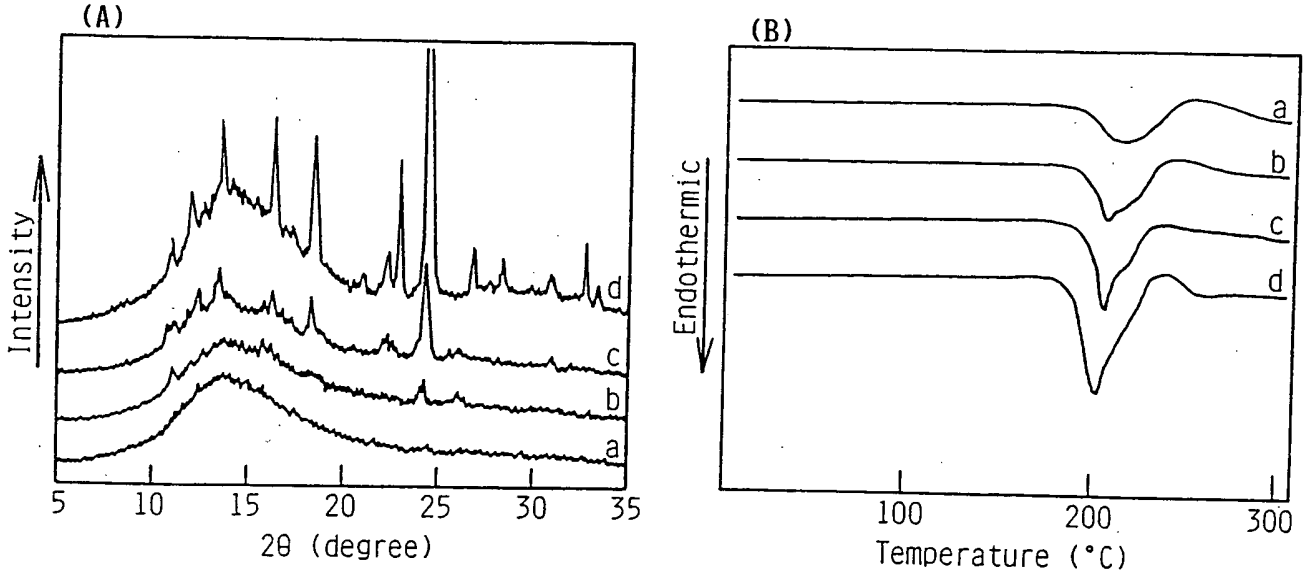

Fig. 3. X-ray powder diffraction patterns (A) and DSC curves (B) of microballoons containing tranilast and Eudragit S in ratios of (a) 1:4, (b) 1:3 and (c) 1:2, and (d) physical mixture (1:4).

peak and the broadened thermogram of microballoons with a weight ratio of drug to polymer=1:4 indicated that the drug was dispersed uniformly at the molecular level (i.e. amorphous) in the shell. The smooth surface of such microballoons might be due to this complete homogeneity of drug and polymer. The minimum amount of Eudragit S incorporated in the formulation to obtain complete amorphism of the drug corresponded to that found in the solid dispersion system reported by Hasegawa et al. [14].

In vitro drug release and floating behavior of microballoons

The rate of drug release from microballoons clearly depended on the polymer concentration formulated in the preparation system (Fig. 4). With increasing the polymer concentration, the drug release rate decreased. The drug release rate was not enhanced by the amorphism even in the pH 7.2 solution, owing to the lower solubility and wettability of the polymer than of the drug in solution. The contact angles of this buffer solution measured by, using a contact anglemeter (CA-A, Kyowa Kagaku Co., Ltd., Japan) positioned against the drug and the polymer film were 45° and 58°, respectively. It was also reported that

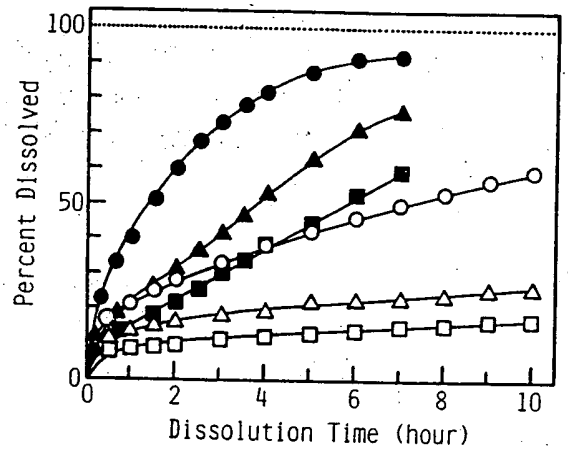

Fig. 4. Dissolution profiles of tranilast from microballoons prepared with various ratios of tranilast to Eudragit S in dissolution medium at pH 6.8 (open symbols) and pH 7.2 (closed symbols). Key: Tranilast:Eudragit S ratio=1:2 (○,●); 1:3 (△,▲); 1:4 (□,■). Size fraction: 500–1000 μm.

the solubility of a drug in the solid dispersion system of Eudragit was not enhanced even if the drug was amorphous [15]. After the drug release test in the medium of pH 6.8, the microballoons were recovered from the system to investigate changes in their morphologies. The shape and internal void of the recovered microballoons were found to be unchanged without disintegra-

tion, but macropores were observed on the surface as illustrated in Figs. 1C and 1D. This finding proved that the shell of the microballoon was a composite film of drug and polymer.

The effect of the size of the microballoons on the dissolution profile is shown in Fig. 5. Unexpectedly, the smaller microballoons released the drug more slowly than larger ones in the dissolution media of pH 6.8 and 7.2 at the initial stage. In general, the faster release rate is obtained with the smaller devices, which possess the larger specific area. This contradictory phenomenon can be explained by the formation of a rigid and hydrophobic shell for the smaller microballoons.

The floating behavior in vitro was investigated in the acidic medium containing a small amount of surfactant (Tween 20; 0.02%, w/v) and agitated with a paddle at 100 rpm, to simulate the wetting action of gastric fluid under movement. It was found that most of the microballoons (buoyancy 80% or above) were still floatable even after 12 h of testing because of their low densities (0.66–0.85 g/cm^3) and owing to the internal voids being completely conserved during the test, as shown in Fig. 6. This finding indicates that the enteric property of the microballoon shell might be advantageous in prolonging the residence time of microballoons in the

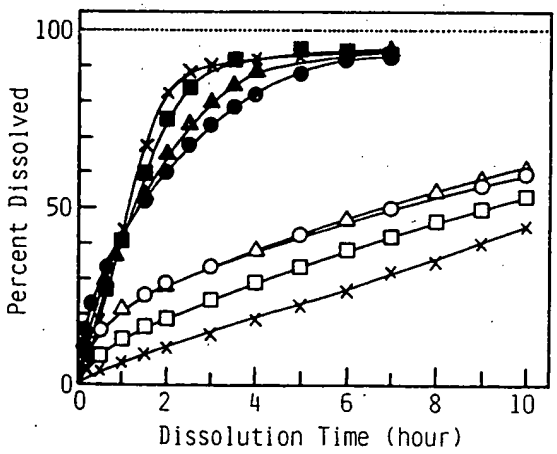

Fig. 5. Dissolution profiles of tranilast from microballoons of various sizes fractionated by the sieving method in a dissolution medium at pH 6.8 (open symbols) and pH 7.2 (closed symbols). Size fractions: (○,●) 500–1000 μm; (△,▲) 297–500 μm; (□,■) 250–297 μm; (×,×) 150–250 μm. Tranilast: Eudragit S ratio = 1:2.

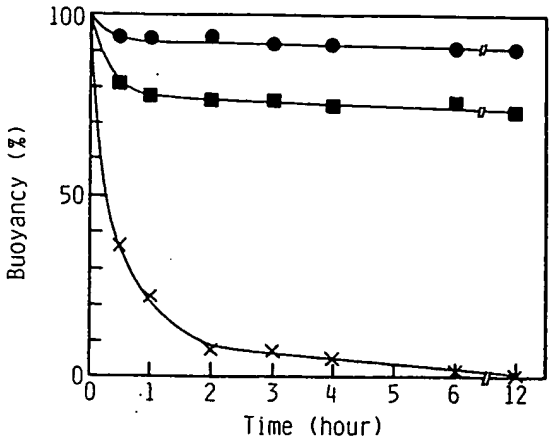

Fig. 6. In vitro floating property of tranilast microballoons (●,■) and control granules (×) in Jap. P. XI No. 1 solution at pH 1.2 containing Tween 20 (0.02%). Size fractions: (●,×) 500–1000 μm; (■) 297–500 μm. Tranilast: Eudragit S ratio = 1:2.

stomach, since dissolution or disruption of the microballoons could be prevented. The microballoon fraction of large size (500–1000 μm diameter) was more floatable than those of smaller size, in line with the particle density (Table 3). The floating properties of the microballoons were clearly evident when compared with the buoyancy of control granules, which had a density of 1.17 g/cm^3 as measured by the displacement method. The control granules settled quickly to the bottom of the flask without disintegration. During the floating test, no swelling or gelation of the microballoons was found, which suggested that they were dispersed individually in the stomach without adhesion to the mucosa. This property should avoid local irritation due to a localized overdose, which frequently occurs with the bioadhesion system.

In vivo floating behavior of microballoons

The floating behavior in vivo was investigated by taking the X-ray photographs of microballoons containing barium sulfate in the stomach. To deepen the radiographical contrast in vivo, sufficient barium sulfate should be enclosed in the microballoon, whereas to improve the floatability of the microballoon less barium sulfate should be enclosed in the device. To meet those

opposing requirements, barium sulfate microballoons having a particle density of 0.92 g/cm^3 were prepared. They were floatable in vitro, although some of them settled owing to the increased density.

It is known that gastrointestinal motility under fasting conditions is characterized by the housekeeper wave, which occurs approximately every 1.5–2 h [7]. This wave may sweep undigested material from the stomach irrespective of its size, shape and density. The floating device works only when there is enough water in the stomach. Therefore the microballoons were administered with 100 ml of water after a light meal, as described in the experimental section.

The series of X-ray photographs of the microballoons with barium sulfate in the stomach are shown in Fig. 7. After administration, the microballoons packed in hard-gelatin capsules immediately floated on the surface of the contents in the stomach, as seen in Fig. 7A. At the early stages, within 60 min after dosing, the microbal-

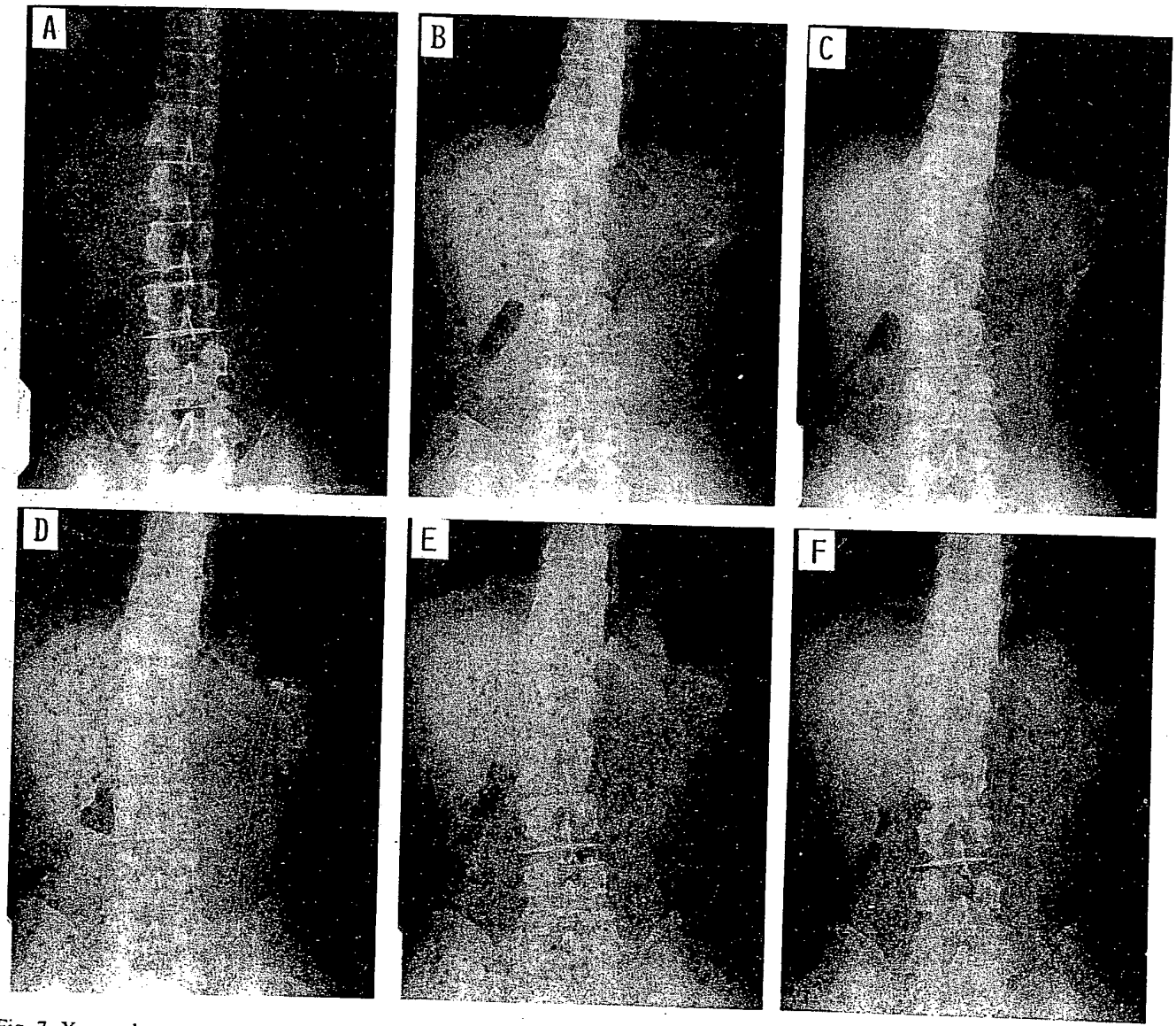

Fig. 7. X-ray photographs of tranilast microballoons (density=0.92 g/cm^3) containing barium sulfate in the gastrointestinal tract at (A) 0 min, (B) 15 min, (C) 30 min, (D) 60 min, (E) 90 min, and (F) 150 min after dosing in the fed state.

loons were found to form two clouds of particles in the upper part of the stomach, as seen in Figs. 7B and 7C. At stages later than 60 min after dosing, the surface of the stomach contents was greatly roughened due to peristaltic movement (Figs. 7D and 7E) compared with the initial stages of Figs. 7A–C. Even under such a peristaltic wave propeling the antral contents towards the pylorus, the microballoons were dispersed in the upper part of stomach, as seen in Fig. 7F. After 80 min, some microballoons still remained, since the present system could delay their arrival at the pylorus. The prolonged residence of microballoons in the stomach might be explained by their floating properties as well as by random emptying effects due to the present multiple-unit system. Because the microballoons were always spread in the upper part of the stomach during the test, as seen in Fig. 7, the present floating system might have less chance of "fortuitous emptying". Mori et al. reported that gastric emptying of granules with a specific gravity of 0.9 could be delayed by their floating properties in rats [16], although such studies may not be directly comparable with the present system.

The microballoons loaded with the drug, being lighter than those with barium sulfate, might be expected to prolong further the gastric emptying time. No deviation between results for the two volunteers was observed. The present formulations of microballoons were composed of enteric multiple-unit devices. Due to their wide spreading over the antrum, the subunits approached to the pylorus might pass through the stomach individually and release the drug at once in the upper gut, leading to decreased variability of drug action among patients compared with that occurring in the case of single-unit dosage forms, e.g. HBS.

This study has suggested that microballoons could be a candidate novel delivery device to improve the bioavailability of tranilast and other compounds which are aimed to produce a local and specific effect in the stomach and are specifically absorbed through the upper region of the small intestine. Further in vivo studies on floating behavior and on drug absorption after oral administration of the microballoons under fed and fasted states should be investigated to clarify the influence of food on the gastric emptying time of microballoons.

Acknowledgements

A part of the present research was supported by a Grant in Aid for General Scientific Research (No. A 01400005) from the Ministry of Education, Science and Culture, Japan. The authors wish to thank Prof. A. Ohtsuka, Meijo University, Nagoya, Japan, for the use of the porosimeter and are grateful to Mr. Shinji Ohmori and Miss Shiho Ihara for their technical assistance.

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